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26. (amended) The method according to claim 24 wherein the substance [is a substance that] normally operates said [product] receptor.

REMARKS

Claims 1-26 are pending in the above referenced application and claims 1-13 stand withdrawn from further consideration. Claims 14-26 stand rejected. Claims 14, 16-19, 21-24 and 26 have been amended to more particularly describe the present invention. No new matter has been added by these amendments. Claims 15, 20 and 25 have been cancelled without prejudice.

A petition for an extension of time of three (3) months for responding to the outstanding Office Action and the appropriate fee authorization is enclosed herewith.

Reconsideration of this application is respectfully requested in view of the above amendment and the following discussion.

Claims 14-26 stand rejected under 35 USC 112, first paragraph. The Examiner states that even though the specification is enabling for a method of screening for a substance that restores normal function to a known receptor with a mutation, it does not reasonably enable a method of screening for a substance that restores normal function to **any** mutant gene product. Applicant respectfully traverses this rejection.

In order to expedite prosecution of the above referenced application, Applicant has amended the claims to recite methods of screening substances for a substance capable of causing an aberrant receptor to operate in a manner similar to a non-aberrant, i.e., wild-type, receptor. The Examiner has admitted that the specification is enabling for a method of screening for a substance that restores normal function to a known receptor with a mutation.

The specification clearly enables the presently claimed invention, which comprises bringing an aberrant receptor into contact with a subject substance and

assaying the operation activity of said substance on said receptor. For example, the specification teaches how to identify an aberrant gene as a disease causing gene, e.g., genes encoding an aberrant receptor, see e.g., pages 21-24, and how to isolate an expression product, e.g., an aberrant receptor, see e.g., pages 25-26. While the complexity of this invention may be high, the level of skill in this art is also high. The specification describes procedures that one of ordinary skill in the art can perform without undue experimentation. The screening procedure is described in detail on pages 26-30 and the method of creating a drug for treatment of a disease caused by an aberrant receptor is set forth on pages 30-33. Finally, Applicant has set forth examples which demonstrate the present invention. One of ordinary skill in the art will readily be able to perform the claimed methods based upon the teachings of the specification and knowledge in the art.

Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Claims 14-26 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully submits that the above claim amendments obviate the Examiner's rejection.

The Examiner states that claims 14, 24 and dependent claims 15, 25 and 26 are vague and indefinite because they recite the term "operating an aberrant gene product", and it is not clear how the substance "operates" the gene product. The Examiner states that the meaning of the term "operating" in the context of claims 14, 16, 20, 21, 26 and dependent claims 15, 18, 19, 22, 23 and 25 is unclear. Applicant respectfully disagrees with the Examiner's position. The specification clearly describes what is meant by the term "operating an aberrant gene product." For example, page 15, lines 19-24 states that

> ...which mutant can cause a disease due to the fact that the reactivity of a substance that **operates** the normal gene product (e.g., the ligand that **operates** the normal receptor, such

> as a natural ligand present in vivo) differs from the reactivity of said substance which [is] the normal gene product. Also, it is preferable that the aberrant gene product and the normal gene product are capable of similar function, i.e., after a substance against the aberrant gene product results in the aberrant gene product **acting** normally, the aberrant gene product should exhibit a response (e.g., change in intracellular concentration of responding substance in the signal transduction system of cells having the normal receptor) similar to that exhibited by an **operating** substance thereagainst.

Thus it is clear that the term "operating" means that the substance "acts on" or "reacts with" the gene product.

Although the Applicant disagrees with the Examiner's position with regard to the term "operating", the Applicant has amended the claims in order to expedite prosecution of the application. Applicant respectfully submits that that the above amendments obviate the Examiner's concerns.

Claims 14-25 stand rejected under 35 USC 102(b) as being anticipated by Lebrun et al. Applicant respectfully traverses this rejection. Lebrun et al. fails to anticipate the present invention for the following reasons.

Lebrun et al. suggest that the extracellular conformation of the mutant (insulin) receptor ($Val^{382}$) and that of the wild type receptor are different (p. 11273, right column, line 26-28 of RESULTS). Lebrun et al. found that the $Val^{382}$ receptor is locked in a conformation that cannot be changed by insulin binding. (p.11274, left column, 1.20 -23). This is in contrast to the wild type insulin receptor, which is known to undergo conformational changes in the β-subunit during its hormone-induced activation, i.e., when bound by insulin. (p.11273, right column, line 29 of RESULT to p. 11274, left column, line 1).

Lebrun et al. show that the mutation in the receptor **does not** affect the **insulin binding activity** and the intrinsic kinase of the $Val^{382}$ receptor is intact (p.11272, right column, 1.31 - 33, p.11274, left column, line 25 - 30). They also teach that

although insulin can bind the receptor, insulin binding to the receptor **cannot simulate** the kinase activity of the mutant receptor (p.11272, right column, line 31 - 33).

Lebrun et al. found that the kinase activity of the insulin-bound $Val^{382}$ receptor could be restored by certain monoclonal antibodies. They found two monoclonal antibodies directed to the receptor extracellular domain, which restore the kinase activity. They concluded that the restoration of the kinase activity by the monoclonal antibodies is due to the appearance of C-terminal conformational changes in the receptor. These conformational changes are similar to the conformational changes normally induced in the wild type receptor by insulin binding alone. (See p. 11272 and p. 11274, right column, line 44 -47).

Thus, the antibody of Lebrun acts like an "enhancer" or "helper", which enables the mutant receptor to act in the presence of insulin binding to the mutant receptor. Thus, the method of Lebrun et al provides a method of screening for an antibody, which can change the conformation of the insulin receptor in the presence of insulin, which binds the insulin receptor even though the receptor is aberrant. This method of action is much different from the presently claimed method of screening for a substance capable of restoring the activity of the receptor.

In contrast to Lebrun, the method of screening of the present invention is performed without adding an "enhancer ligand" (e.g., Lebrun's antibody), and is directed to screening for a substance which is capable of operating a mutant receptor by itself, such as an agonist or an antagonist. See specification, page 26, line 25 - page 30, line 13). Furthermore, the methods of the present invention can select a substance capable of restoring the activity of a mutant receptor without changing the conformation of the receptor, in contrast to the mechanisms described in Lebrun et al.

It is clear from the specification that the methods of the present invention comprises an aberrant receptor which has a mutation which results in a changed affinity for substances such as the natural ligand, i.e., the receptor will not operate in

the presence of the natural ligand. The specification further teaches that the methods screen for compounds that cause the aberrant receptors to operate like the non-aberrant receptor. As described in the present specification, at page 16, lines 13-34, an "aberrant receptor" is described as including

> receptors with a mutation in the structural gene thereof in vivo, resulting in **substantially changed affinity for substances such as the natural ligand** (e.g., reduction, enhancement etc., preferably reduction), particularly receptors that cause a disease due to the substantial change in the affinity of said natural ligand. The term "substantial change" as used above means a change to the extent that a disease can be caused when **the affinity of the natural ligand for the normal and aberrant receptors are compared**, and may be any change, whether significant or insignificant, as long as it is capable of causing a disease. Also, it is preferable that the aberrant receptor and the normal receptor be capable of similar function, i.e., after an operating substance against the aberrant receptor results in the aberrant receptor acting normally, the aberrant receptor should exhibit a response (e.g., change in intracellular concentration of responding substance in the signal transduction system of cells having the normal receptor) similar to that product by the normal receptor after being operated by a natural ligand thereagainst.

Thus, the methods disclosed in Lebrun et al., in which the mutant receptor is still capable of binding the natural ligand, and the "substance", i.e., the antibodies, act as an enhancer, are substantially different from the present invention. Lebrun, therefore, fails to anticipate the present invention. The applicant respectfully requests reconsideration and withdrawal of this rejection.

In view of the discussion above, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited. Should the Examiner wish to discuss the above amendment made herein, the undersigned attorney would appreciate the opportunity

to do so. Thus the Examiner is hereby invited to call the undersigned, collect at the number shown below.

Respectfully submitted,

Date: July 13, 2000

Cara Z. Lowen
Reg. No. 38,227

Dike, Bronstein, Roberts & Cushman
Intellectual Property Practice Group
EDWARDS & ANGELL, LLP
130 Water Street
Boston, MA 02109
(617) 523-3400
133749